

maintenance of labor and in the regulation of bone resorption (see, for example, D. M. Slater et al., in *Am. J. Obstet. Gynecol.*, 172:77-82 (1995); and Y. Onoe et al., in *J. Immunol.* 156:758-764 (1996)), thus inhibition of this pathway may not always be beneficial. Considering these points, highly selective COX-2 inhibitors may produce  
5 additional side effects above and beyond those observed with standard NSAIDs, therefore such inhibitors may not be highly desirable.

Indeed, recent studies with first generation COX-2 inhibitors reveal that arthritic patients treated with rofecoxib had a five-fold higher risk of heart attack, compared to  
10 patients treated with naproxen (*Wale St. Jnl*, 5/1/10). Thus, like aspirin, naproxen appears to exert cardioprotective effects, while selective COX-2 inhibitors do not.

Accordingly, there is still a need in the art for modified forms of NSAIDs, and other pharmacologically active agents, e.g., selective COX-2 inhibitors, which cause a  
15 reduced incidence of side-effects, relative to the incidence of side-effects caused by such pharmacologically active agents in unmodified form.

### BRIEF DESCRIPTION OF THE INVENTION

20 In accordance with the present invention, there are provided conjugates of a combination of pharmacologically active agents (e.g., NSAIDs and selective COX-2 inhibitors). Invention conjugates (e.g., NSAID-COX-2<sup>i</sup>) provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which provide the therapeutic benefits of both NSAIDs and selective COX-2 inhibitors, while causing a  
25 much lower incidence of side-effects than are typically observed with such agents due to the protective effects imparted by modifying the pharmacologically active agents as described herein.

There are a number of advantages of conjugates according to the invention (e.g.,  
30 NSAID-COX-2<sup>i</sup>), including:

(i) reduced irritant effects (e.g., contact irritation) of NSAIDs and COX-2

inhibitors, and

(ii) enhanced tissue delivery of both drugs as a result of a decrease in net charges on the molecule, particularly for acidic NSAIDs such as naproxen, aspirin, diclofenac and ibuprofen, thereby reducing the quantity of material which must be delivered to achieve an effective dosage.

In accordance with the present invention, cleavage of the novel bio-cleavable conjugates described herein releases both components thereof as active pharmaceutical agents.

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### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds comprising a conjugate wherein a NSAID is covalently attached to a selective COX-2 inhibitor. Invention compounds have the structure:

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wherein:

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X = a non-steroidal anti-inflammatory drug (NSAID),

L = an optional linker/spacer, and

Y = a selective COX-2 inhibitor.

Invention compounds can be readily prepared in a variety of ways, e.g., by direct reaction of NSAIDs with COX-2 inhibitors, or by indirectly linking NSAIDs to COX-2 inhibitors employing a suitable linker/spacer.

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The components of invention conjugates are directly or indirectly covalently attached employing a variety of linkages (including an optional linker), e.g., ester linkages, disulfide linkages, amide linkages, imine linkages, enamine linkages, ether linkages, thioether linkages, imide linkages, sulfate ester linkages, sulfonate ester

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linkages, sulfone linkages, sulfonamide linkages, phosphate ester linkages, carbonate linkages, O-glycosidic linkages, S-glycosidic linkages, and the like. Such linkages can be accomplished using standard synthetic techniques as are well known by those of skill in the art, either by direct reaction of the starting materials, or by incorporating a suitable functional group on the starting material, followed by coupling of the reactants.

When the pharmacologically active agents contemplated for use herein contain suitable functionality thereon, e.g., hydroxy, amino, carboxy, and the like, invention conjugate can be prepared by direct linkage between the two agents. Alternatively, one or both of the pharmacologically active agents can be functionalized so as to facilitate linkage between the two agents. When present, linker/spacer L has one of the following structures:

-Z-W-,  
-W-Z-, or  
-W-Z-W-

wherein:

Z is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

each W is independently ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, sulfone, sulfonamide, immine, enamine, or the like.

As employed herein, "alkylene" refers to divalent hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkylene" comprises alkylene groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl,

cyano, nitro, nitron, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfonyl, and the like.

As employed herein, "cycloalkylene" refers to cyclic ring-containing groups  
5 containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkylene" refers to cycloalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups  
10 containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "oxyalkylene" refers to the moiety -O-alkylene-, wherein  
15 alkylene is as defined above, and "substituted oxyalkylene" refers to oxyalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkenylene" refers to divalent, straight or branched chain  
20 hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenylene" refers to alkenylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkynylene" refers to divalent straight or branched chain  
25 hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynylene" refers to alkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylene" refers to divalent aromatic groups having in the  
30 range of 6 up to 14 carbon atoms and "substituted arylene" refers to arylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkylarylene" refers to alkyl-substituted arylene groups and "substituted alkylarylene" refers to alkylarylene groups further bearing one or more substituents as set forth above.

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As employed herein, "arylalkylene" refers to aryl-substituted alkylene groups and "substituted arylalkylene" refers to arylalkylene groups further bearing one or more substituents as set forth above.

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As employed herein, "arylalkenylene" refers to aryl-substituted alkenylene groups and "substituted arylalkenylene" refers to arylalkenylene groups further bearing one or more substituents as set forth above.

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As employed herein, "arylalkynylene" refers to aryl-substituted alkynylene groups and "substituted arylalkynylene" refers to arylalkynylene groups further bearing one or more substituents as set forth above.

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Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma, carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS,

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AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.

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NSAIDs contemplated for modification in accordance with the present invention include acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen, others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (Iodine), fenoprofen calcium (nalfon), flurbiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), carprofen, indoprofen, ketorolac tromethamine (toradol), magnesium salicylate (Doan's, magan, mobidin, others), meclofenamate sodium (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzonate, salsalate, tiaprofenic acid, flosulide, and the like. Presently preferred NSAIDs employed in the practice of the invention include naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, carprofen, and the like.

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Selective COX-2 inhibitors contemplated for modification in accordance with the present invention include celecoxib, rofecoxib, valdecoxib, and the like, as well as analogs, homologs and derivatives thereof.

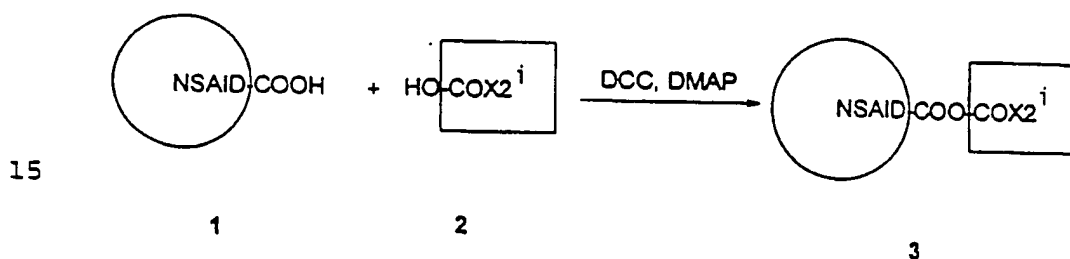
In accordance with another embodiment of the present invention, there are provided methods for the preparation of protected forms of pharmacologically active agents, said method comprising covalently attaching two defined pharmacologically

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active agents to one another. The resulting conjugate provides a latent form of each of the pharmacologically active agents, releasing the biological activity thereof only when the conjugate is cleaved (e.g., by an esterase, amidase or other suitable enzyme).

5 As readily recognized by those of skill in the art, invention conjugates can be prepared in a variety of ways. See, for example, Scheme 1, wherein a NSAID (1) bearing a carboxylic moiety can be reacted with a hydroxy substituted COX-2 inhibitor (2) under conditions suitable to produce invention conjugate (3).

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SCHEME 1

20 Employing this general reaction scheme, invention conjugates can be prepared from a wide variety of pharmacologically active agents. See, for example, Examples 1-13 provided herein.

25 In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of NSAIDs to a subject, said method comprising covalently attaching a selective COX-2 inhibitor to said NSAID prior to administration to said subject.

30 In accordance with a further embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of selective COX-2 inhibitors to a subject, said method comprising covalently attaching a NSAID to said selective COX-2 inhibitor prior to administration to said subject.

In accordance with still another embodiment of the present invention, there are provided methods for enhancing the effectiveness of NSAIDs, said method comprising covalently attaching a selective COX-2 inhibitor to said NSAID.

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In accordance with yet another embodiment of the present invention, there are provided methods for enhancing the effectiveness of selective COX-2 inhibitors, said method comprising covalently attaching a NSAID to said selective COX-2 inhibitor.

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In accordance with a still further embodiment of the present invention, there are provided improved methods for the administration of NSAIDs and/or selective COX-2 inhibitors to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching said NSAID to said selective COX-2 inhibitor prior to administration thereof to said subject.

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Those of skill in the art recognize that the conjugates described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

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Depending on the mode of delivery employed, the conjugates contemplated for use herein can be delivered in a variety of pharmaceutically acceptable forms. For example, the conjugate can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

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Thus, in accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) comprising invention conjugates in a suitable vehicle rendering said conjugates amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.